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Hypertrophic pachymeningitis, IgG4-related disease: case report

Paquimeningite hipertrófica, doença relacionada com a IgG4: relato de caso

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ABSTRACT

The IgG4-related disease (IgG4-RD) is a systemic disease recently characterized as an inflammatory condition generally related to the increase in serum IgG4 levels, a subclass of immunoglobulins (IgG) which corresponds to less than 6% of the total serum IgG, with singular histopathological features. The involvement of the central nervous system is rare and may be isolated or associated with other organs, mimicking tumors. Commonly, it involves the hypophysis, presenting hypophysitis as the main manifestation, but it can also affect the dura mater, presenting as IgG4-related hypertrophic pachymeningitis (IgG4-RHP). Neurological manifestations occur as a result of mass effect, typically due to vascular or nervous structures compression, resulting in functional deficits according to the anatomical site of the lesion. The main histopathological features are dense lymphoplasmacytic infiltrate, fibrosis arranged, at least focally, in a storiform pattern, and obliterative phlebitis, associated with increased numbers of IgG4+ plasma cells or an increased IgG4/IgG ratio in tissue. In this disease, the serum IgG4 levels are usually increased. The objective of this article is to report the case of a 37-year-old male patient who presented a pulsatile headache associated with diplopia and blurred vision. After radiological, histopathological and immunohistochemical studies, the diagnosis of IgG4-RHP was confirmed, besides presenting a literature review about IgG4-RD and IgG4-RHP.

Key words: immunoglobulin G4-related disease; central nervous system; meninges.

RESUMO

A doença relacionada com a imunoglobulina G4 (DRIgG4) é uma enfermidade sistêmica recentemente caracterizada como condição inflamatória que se relaciona com o aumento sérico de IgG4, uma subclasse de imunoglobulinas (IgG) que compreende menos de 6% do total de IgG séricas, com características histopatológicas singulares. O acometimento do sistema nervoso central (SNC) é raro e pode ser isolado ou associado a outros órgãos; é muito confundido com tumores. É mais comum na hipófise, sendo a hipofisite sua principal manifestação, mas pode acometer também a dura-máter, manifestando-se como paquimeningite hipertrófica associada à IgG4 (PH-DRIgG4). As apresentações neurológicas são creditadas ao efeito de massa, tipicamente por compressão de estruturas vasculares ou nervosas, propiciando déficits funcionais de acordo com o sítio anatômico da lesão. Os achados histológicos mais comuns são infiltrado linfoplasmocitário denso, fibrose (em arranjo, pelo menos focalmente, de padrão estoriforme), e flebite obliterativa, além de elevação do número de plasmócitos IgG4+ ou da razão IgG4/IgG no tecido. Nessa doença, os níveis séricos de IgG4 geralmente estão elevados. O objetivo deste artigo é relatar o caso de um paciente do sexo masculino com quadro de cefaleia pulsátil associada à diplopia e turvação visual. Após estudo radiológico, histopatológico e imuno-histoquímico, foi obtido o diagnóstico de PH-DRIgG4. Apresentamos, ainda, uma revisão de literatura sobre DRIgG4 e PH-DRIgG4.

Unitermos: *doença relacionada com a imunoglobulina G4; sistema nervoso central; meninges.*

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RESUMEN

La enfermedad relacionada con inmunoglobulina G4 (ER-IgG4) es una enfermedad sistémica recientemente caracterizada como condición inflamatoria que se relaciona con el aumento sérico de IgG4, una subclase de inmunoglobulinas (IgG) que incluye menos de 6% del total de IgG séricas, con características histopatológicas propias. El acometimiento del sistema nervioso central (SNC) es raro y puede ser aislado o asociado a otros órganos; es muy confundido con tumores. Es más común en la hipófisis, siendo la hipofisitis su principal manifestación, pero puede acometer también la duramadre, manifestándose como paquimeningitis hipertrófica relacionada con IgG4 (PHR-IgG4). Las presentaciones neurológicas se atribuyen al efecto de masa, típicamente por compresión de estructuras vasculares o nerviosas, produciendo déficits funcionales según la ubicación anatómica de la lesión. Los hallazgos histológicos más comunes son infiltrado linfoplasmocítico denso, fibrosis (disposta, por lo menos focalmente, en un patrón estoriforme) y flebitis obliterante, además de elevación del número de células plasmáticas IgG4+ o de la proporción IgG4/IgG en el tejido. En esa enfermedad, los niveles séricos de IgG suelen estar elevados. El objetivo de este trabajo es reportar el caso de un paciente masculino con cuadro de cefalea pulsátil asociada a diplopía y visión borrosa. Luego de estudio radiológico, histopatológico y inmunohistoquímico, se obtuvo el diagnóstico de PHR-IgG4. Aún presentamos una revisión de literatura sobre la ER-IgG4 y la PHR-IgG4.

Palabras clave: *enfermedad relacionada con inmunoglobulina G4; sistema nervioso central; meninges.*

INTRODUCTION

The immunoglobulin G4-related disease (IgG4-RD) is a systemic involvement recently characterized as an inflammatory condition[1]; it is generally related to the increase in serum immunoglobulin G4 (IgG4), a subclass of immunoglobulin that comprises less than 6% of the total serum IgG[2], with unique histopathological characteristics[1, 3]. The involvement of the central nervous system (CNS) is rare – when it happens, it is more common in the pituitary gland – the main manifestations are IgG4-RD hypophysitis and hypertrophic pachymeningitis (HP)[4].

This study presents the case report of a patient with IgG4-related hypertrophic pachymeningitis (IgG4-RHP), with radiological correlation and immunophenotypic confirmation, in addition to a review of the literature on the subject.

CASE REPORT

Male patient, 37 years old, with pulsatile headache in the right temporal region, which started about two years ago, of moderate intensity and worsening with physical effort, but relieving to conventional analgesia.

After clinical worsening, it evolved with increased pain and the presence of diplopia and blurred vision. He sought medical attention; on physical examination, mydriasis, non-reactive right pupil, III and IV cranial pairs palsy, and right lateral rectus muscle paralysis were found; no other findings on examination were observed.

The patient underwent radiological study by magnetic resonance imaging (MRI), which showed a retroclival meningeal lesion with marked T2 hyposignal and brain stem compression, causing edema; there was also an intense contrast enhancement of the lesion (**Figure 1**).

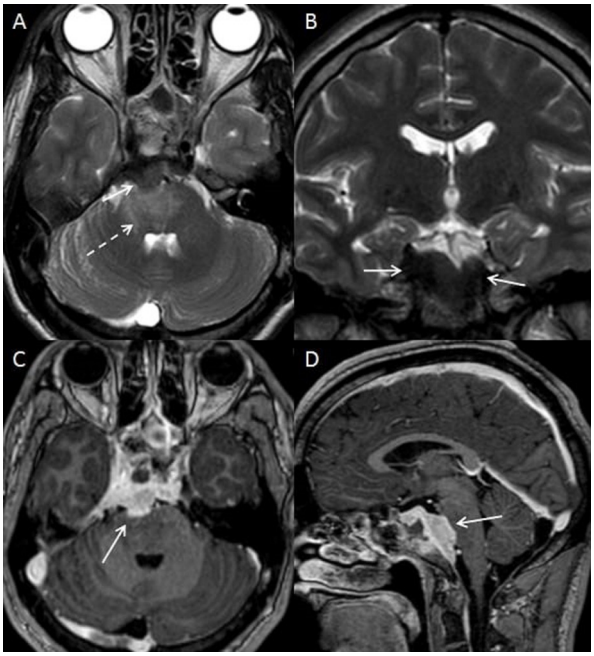

FIGURE 1 – *Images obtained from the magnetic resonance exam*

Axial T2 (A), coronal T2 (B), axial T1 post-contrast (C), and sagittal T1 post-contrast (D) sequences. Retroclival meningeal lesion with marked hyposignal on T2 (arrows in A and B); there is compression on the brain stem, causing edema, with hypersignal on T2 (dashed arrow in A); there is an intense contrast enhancement on T1 sequences by the lesion (arrows in C and D).

Source: prepared by the author.

The transsphenoidal biopsy of the lesion showed a marked lymphoplasmacytic inflammatory process with storiform fibrosis, obliterative phlebitis, and occasional eosinophils associated in the dura mater (**Figures 2** to **5**). The immunohistochemical study showed a predominance of IgG4+ plasma cells, with about 40 IgG4+ plasma cells per high-power field (hpf). The patient did not present high levels of autoantibodies, and serum IgG4 levels were within the normal range. The immunophenotypic profile of the lesion associated with imaging exams and patient's clinical condition enabled the diagnosis of IgG4-RHP to be completed (**Figures 6** and **7**).

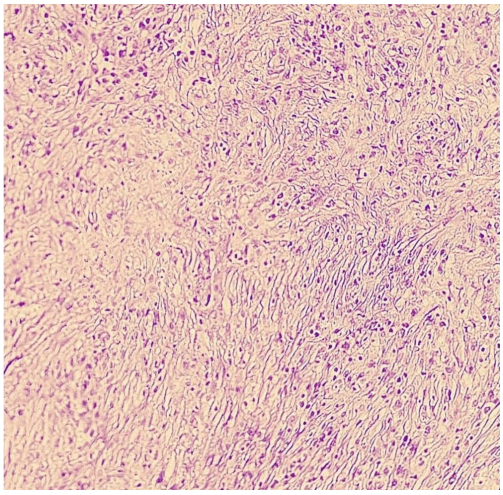

FIGURE 2 – *Photomicrograph showing extensive areas of storiform pattern fibrosis. HE staining, 100× magnification*

Source: prepared by the author.
HE: hematoxylin and eosin

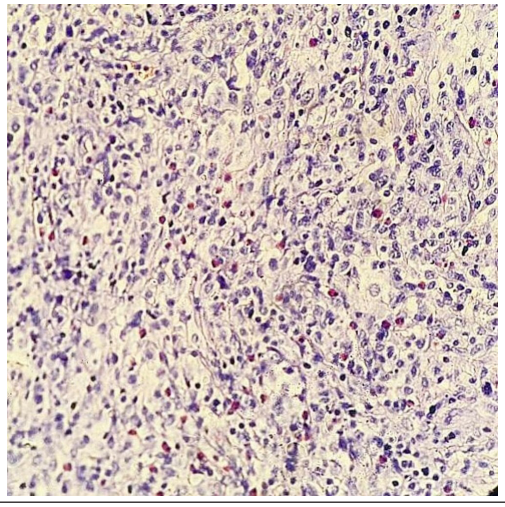

FIGURE 3 – *Photomicrography showing lymphomononuclear infiltrate, with an emphasis on the presence of occasional eosinophils associated. HE staining, 200× magnification*

Source: prepared by the author.
HE: hematoxylin and eosin.

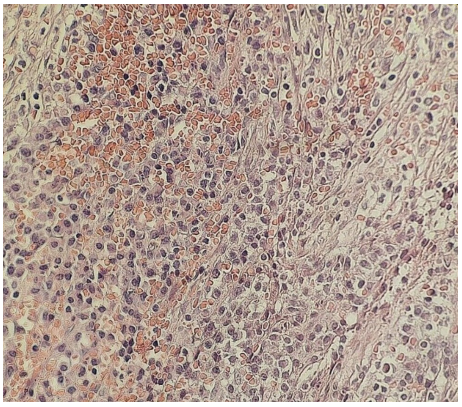

FIGURE 4 – *Photomicrograph of areas of the lesion that exhibit intense lymphoplasmacytic infiltrate. HE staining, 200× magnification*

Source: prepared by the author.
HE: hematoxylin and eosin.

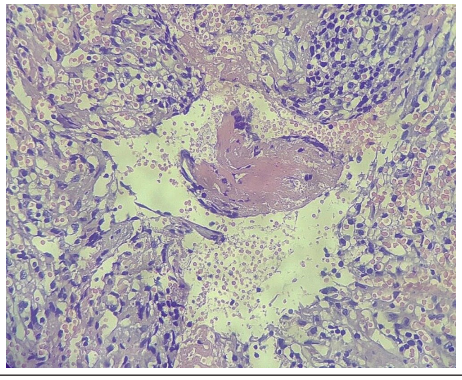

FIGURE 5 – *Photomicrograph showing obliterating phlebitis represented by a venular vessel with aggression by vessel with lymphomononuclear cells aggression and fibrinous and organized thrombus formation that partially occludes the vessel lumen. HE staining, 100× magnification*

Source: prepared by the author.
HE: hematoxylin and eosin

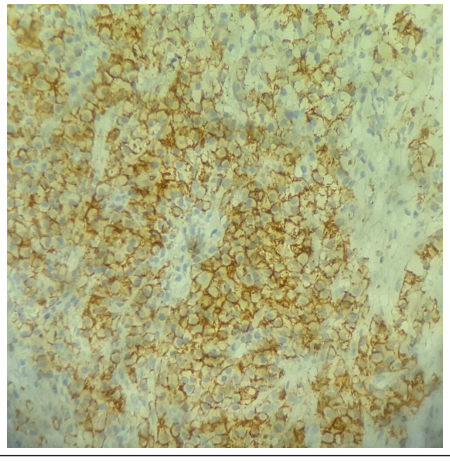

FIGURE 6 – *Photomicrography in an area of dense lymphoplasmacytic infiltrate revealing diffuse immunoexpression for anti-CD138 antibody. Immunohistochemistry technique for anti-CD138 antibody, 200× magnification*

Source: prepared by the author.

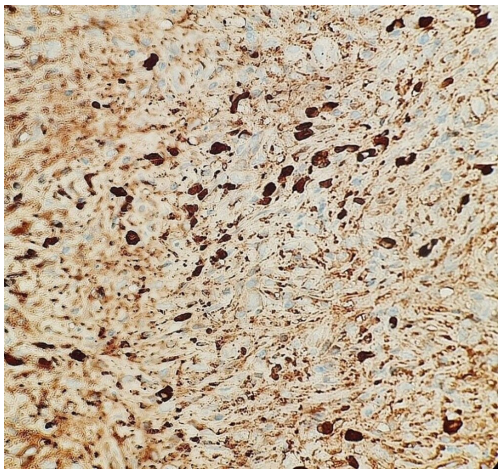

FIGURE 7 – *Photomicrograph showing a predominance of IgG4 positive plasma cells. Immunohistochemistry technique for anti-IgG4 antibody, 200× magnification*

Source: prepared by the author.
IgG4: immunoglobulin G4.

After two weeks of oral corticosteroid therapy, the patient evolved with significant clinical improvement. There was complete remission of symptoms after four weeks of treatment. He is asymptomatic and has been followed at the neurology service for six months since the end of corticosteroid therapy.

DISCUSSION

IgG4-RD was initially recognized by Hamano *et al*., in 2001 and 2002, as the association between autoimmune pancreatitis and increased serum IgG4[5, 6]; however, over the years, it has been linked to other diseases, such as cholangitis, sclerosing sialadenitis, retroperitoneal fibrosis, interstitial pneumonia Sjögren's syndrome, primary biliary cirrhosis, multifocal fibrosclerosis, neurosyphilis, tuberculosis, fungal meningitis, and rheumatoid arthritis[5-7].

CNS involvement is rare and can be isolated or associated with other organs; it is mistaken for tumors[8]. It is more common in the pituitary gland; hypophysitis is its main manifestation. When it affects the dura mater, it manifests as IgG4-RHP [4].

IgG4-RDs occur, predominantly, in men aged between 50 and 60 years[9], who generally have hypergammaglobulinemia and high levels of autoantibodies[10-12]. Elevated serum IgG4 levels are present in 70%-90% of patients[13]. In our report, serum IgG and IgG4 levels were normal.

The IgG4-RD and IgG4-RHP pathogenesis is still unclear. However, it is believed that the inflammatory infiltrate, rich in B and T lymphocytes, activates fibroblasts and induces collagen deposition, causing thickening of the dura mater, the main affected meninge[13, 14]. Recent studies support the concept that IgG4-RD is an antigen-driven disease, involving actions of T cells and autoreactive mutated B cell lines, which could contribute to the fibrous process through mechanisms that have not yet been elucidated. IgG4 antibodies are usually considered non-inflammatory, which makes it difficult to define their role in the disease process[15].

De Virgilio e*t al*. (2017)[14], in a review of a IgG4-RHP case series, show that neurological presentations are credited to the mass effect, typically by compression of vascular or nervous structures, providing functional deficits according to the anatomical site of the lesion. Among the signs and symptoms, the following are included, in decreasing order of involvement: headache; cranial nerve dysfunction and ophthalmopathy, such as diplopia and decreased visual acuity. When the lesion occurs in the anterior cranial fossa, it can manifest as retro-orbital pain and disorders that affect the eyesight and eye movement, usually as Tolosa-Hunt syndrome[14]. In this study, the patient presented headache, diplopia and blurred vision associated with the III and IV cranial nerve pairs palsy and right lateral rectus muscle paralysis. Other clinical manifestations reported in the literature are paresis, paresthesia, sensorineural hearing impairment and seizures[13, 16]. Although they reflect such compression mechanisms, the clinical manifestations of IgG4-RHP are not distinguishable from other forms of HP[13].

Due to the rarity of the disease, the radiological aspects described in the literature are incipient and not fully established; a IgG4-RHP is an unusual pathology characterized by thickening, localized or diffuse, linear or as a protruding mass, of the dura mater[14]. Dziedzic *et al*. (2015)[16], in a case report and literature review, point out that the most common findings on MRI include, in addition to thickening of the dura mater, hypointense signal on T1 and T2 sequences, demonstrating an active inflammatory process at the limits of dura mater in postcontrast T1 sequences. In our study, the patient presented thickening of the dura in the clivus, with marked hyposignal in T2, which caused compression on the brain stem and caused vasogenic edema (Figure 1). In computed tomography (CT) studies, on the other hand, although the radiological findings are not specific for IgG4-RD, the lesions can appear thickened and hyperdense, and are highlighted after administration of iodinated contrast[16-18].

Acute phase markers, such as erythrocyte sedimentation rate and C-reactive protein, are usually elevated at a moderate level. Elevated serum immunoglobulin E (IgE) levels are also observed in some patients. In general, cerebrospinal fluid analysis reveals a

clear appearance with normal glucose concentration, in addition to normal to slightly increased protein content and variable degree of lymphocytic pleocytosis[13, 19].

Deshpande V *et al*. (2012), in the article *Consensus statement on the pathology of IgG4-related disease*, defined as IgG4-RD histopathological characteristics: dense lymphoplasmacytic infiltrate, fibrosis arranged at least focally in a storiform pattern, and obliterative phlebitis; the presence of least two of these characteristics is necessary for a reliable pathological diagnosis, in addition to an increase in the number of IgG4+ plasma cells or the IgG4/IgG ratio in the tissue. Other elements, such as phlebitis with no obliteration of the lumen and an increased number of eosinophils, are associated with IgG4-RD, and are neither sensitive nor specific for diagnosis when isolated[20].

The cut-off point considered for the IgG4+ plasma cell count ranges from 10 to 200 hpf according to the affected organ; with regard to meninges, a value greater than 10 IgG4+ plasma cells/hpf was adopted[20].

Several authors consider the ratio between IgG4+ plasma cells/IgG+ as a reliable criterion for immunohistochemical diagnosis. A cut-off point greater than 40% is considered for the diagnosis of any organ, in the presence of histopathological features[21, 22]. There are other diseases, regardless IgG4-RD, which are also associated with the high number of IgG4+ plasma cells/hpf, such as inflammatory diseases, lymphoma, and neoplasms[22].

Carruthers M *et al*. (2012)[23] developed an IgG4-RD response index that can be useful when estimating disease activity and assessing response to treatment, which assesses disease activity in potential target organs, as well as the need for emergency treatment , target organ damage, serum IgG4 concentration, and recent use of glucocorticoids[23, 24].

Currently, glucocorticoids are considered the therapy of choice for IgG4-RHP, as well as for other IgG4-RD[18]. Despite its effectiveness in most cases, recurrence rates are high when there is a dose reduction or treatment interruption. Rituximab, methotrexate, mycophenolate mofetil, and cyclophosphamide are used to treatment maintenance after glucocorticoids therapy, however, they are not effective in inducing remission in isolated use[24]. In our study, the patient had a good response to oral corticosteroid therapy, with remission of the condition four weeks after the beginning of treatment and with no symptoms during six months of follow-up.

CONCLUSION

IgG4-RD is a rare disorder, of pathogenesis not yet fully understood, that can affect the CNS; it can affect it in isolation or be associated with other organs. It is often mistaken for tumors. It is important to consider this diagnosis in lesions that manifest as hypophysitis or hypertrophic pachymeningitis, to establish an appropriate immunosuppressive treatment. The lesion immunophenotypic aspects, together with the radiological study and laboratory tests, allow corroborating the diagnosis of this disease. This entity gains wide importance in the current neuropathology scenario, as it is an inflammatory disorder with excellent response to corticosteroid therapy and present favorable prognosis.

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